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Patent Application
Attorney Docket No.PC22013AADO

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By Eileen M Beane
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: ALASDAIR M. NAYLOR, ET AL.

APPLICATION NO.: 10/017,273 : Examiner: Not Yet Assigned

FILING DATE: DECEMBER 12, 2001 : Group Art Unit: Not Yet Assigned

TITLE: TREATMENT OF MALE SEXUAL DYSFUNCTION :

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DECLARATION OF SHERRY L. JENKINS

My name is Sherry L. Jenkins. I hereby declare as follows:

1. On December 12, 2001, and for 9 years prior thereto, I was employed by Pfizer, Inc. in Groton, Connecticut.

2. I am currently still employed by Pfizer, Inc.

3. In summary, I printed an original version of the specification for the above-identified application from my computer, verified that it contained pages 1 through 140, including pages 123 and 124, and submitted this specification to the USPTO via Express Mail. The details follow herein.

4. On or shortly after November 15, 2001, I received a set of "nonprovisional filing papers" for the above-identified patent application, including both a paper and electronic copy of the above-identified application including specification, sequence listing and drawing. I also received a signed Combined Declaration and Power of Attorney form from Mr. David Wood and Ms. Amanda Dunk of our Pfizer, Inc. Sandwich, England facility.

5. On December 12, 2001, at the direction of Attorney A. Dean Olson, I prepared a packet of nonprovisional application filing papers, including a specification that contained a description, claims, and an abstract totaling 140 pages of text, for our file, docket number PC22013AADO. The title of the application is "Treatment of Male Sexual Dysfunction." The inventors are Alasdair Mark Naylor, Pieter Hadewijn van der Graaf and Christopher Peter Wayman.

6. On December 12, 2001, when assembling the various documents to be filed as part of the nonprovisional application papers, I printed an original version of the 140-page specification from my computer printer

7. On December 12, 2001, I personally verified each page of the specification had printed in a readable fashion and that each and every page was present (i.e. printed). After reviewing each page, I retained a copy of same for our file.

8. The copy of the 140-page specification that I retained for our file is complete and pages 123 and 124 are present in our file copy. A copy of said document is enclosed herewith.

9. On December 12, 2001, I used United States Express Mail to submit the nonprovisional application papers (including the specification) to the United States Patent Office.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statement and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of said application Serial No. 10/017,273 or any patent issuing thereon.

Signed at Groton, Connecticut, this 23rd day of May 2002.

Respectfully submitted,

Sherry L. Jenkins

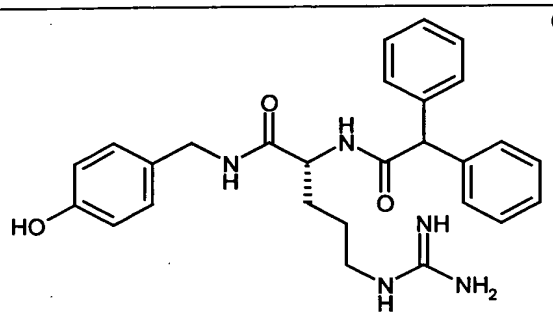
(iv) doses of PDE5 inhibitor we observe a maximal potentiation of ICP, the finding that the ICP can be further potentiated beyond this maximal PDE5 inhibitor mediated is highly unexpected. This illustrates that there are a number of clinical benefits of concomitant administration of a PDE5 inhibitor and a NPY Y1 receptor inhibitor over PDE5 inhibitor therapy alone. These include increased efficacy and opportunities to treat MED subgroups that do not respond to PDE5 inhibitor therapy.

NPY Y1 receptor antagonists and PDE5 or combinations of the two, have no significant effect on un-stimulated ICP i.e. they do not directly induce an increase in ICP in the absence of sexual drive/arousal. This is highly advantageous as the only other marketed therapy for MED which requires sexual stimulation to work is sildenafil thus the present invention provides a viable alternative oral therapy to sildenafil and all other PDE5 alone based drugs.

NPYi - ANIMAL MODEL EXAMPLES

Compounds used in Examples 1 to 6:

NPY receptor antagonist: BIBP 3226

Chiral 	NPY Y1 antagonist Available from Dr Karl Thomae GmbH (Formerly Boehringer Ingelheim Pharma KG) BIBP-3226 WO-09417035

BIBP3226 has an IC50 against human native NPY Y1 = 7nM, selectivity for NPY Y1 (human) over NPY Y5 (human) is greater than 1000, and NPY Y1 selectivity over NPY Y2 (human) is greater than 1000. (See Rudolf *et al* (1994) and Jacques *et al* (1995)).

PDE5i:3-ethyl-5-{5-[4-ethylpiperzino)sulphonyl-2-propoxyphenyl}-2-(2-pyridylmethyl)-6,7-dihydro-2H-pyrazolo[4,3-*d*]pyrimidin-7-one also known as 3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphrenyl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO98/491066). IC50 against human native

PDE5=1.1nM, selectivity for PDE5 over PDE3 (both on native human) is greater than 90,000 and selectivity over PDE4 is 18,545.

All potency and selectivity values quoted are with respect to the human native enzyme (see assays herein).

Example 1. Inhibition of NPY Y1 receptors dose-dependently potentiates nerve stimulated increases in intracavernosal pressure in anaesthetised rabbit model of erection.

Submaximal increases in intracavernosal pressure (ICP) induced by nerve-stimulation were significantly increased in the presence of increasing doses of a selective NPY Y1 receptor antagonist (BIBP3226) (iv bolus). The increase became significant at doses of 30μg/kg and above. The maximal potentiation (circa 127%) was observed at 30μg/kg. Data is expressed as the percentage (%) increase, compared to control stimulated increases. Values are expressed as mean ± s.e.mean. * $P<0.05$, Students t-test unpaired compared with control increases. (See Figure 1)

There were no major effects of NPY Y1 receptor antagonism on basal/un-stimulated intracavernosal pressure.

Example 2. PDE5 inhibition significantly increases the efficacy of PDE5 inhibitor to enhance penile erection in an anaesthetised rabbit model of erection.

Intravenous administration of a selective PDE5 inhibitor (1 mg/kg) significantly enhanced nerve-stimulated increases in ICP by 133±22% compared to control increases. Data is expressed as percentage increase in ICP over control increases. Values are expressed as mean ± s.e.mean. * $P<0.01$, Students t-test unpaired compared with control increases. (See Figure 2)

There were no effects of PDE5 inhibition on basal/un-stimulated intracavernosal pressure.